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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,641	08/30/2001	Philip A. Beachy	JHUC-P01-017	9388
28213	7590	07/11/2007	EXAMINER	
DLA PIPER US LLP 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133			CHANDRA, GYAN	
ART UNIT		PAPER NUMBER		1646
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	09/943,641	BEACHY ET AL.
Examiner	Art Unit	
Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 18 April 2007.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,4,5,8-23 and 26-32 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1,4,5,8-23 and 26-32 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____	6) <input type="checkbox"/> Other: _____

Re: Beachy et al

Date of Priority: 8/30/2000 (US 60/229,243)

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/18/2007 has been entered.

Status of Application, Amendments, And/Or Claims

Claims 1, 4, 5, 8-23 and 26-32 are pending and under examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4, 5, 8-17, 19-23, and 29-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Parnot et al (Proc. Natl. Acad. Sci. 97: 7615-7620, 2000, published on 6/20/2000).

Claims 1, 4, 5, 8-17, 19-23, and 29-32 are broadly a method of identifying constitutively activating mutations in a receptor or an ion channel, comprising (A)

providing a library of coding sequences for potentially activating mutations of a G protein coupled receptor or ion channel, which library is generated by replacing coding sequences for small or medium side-chain amino acids, wherein the mutation is conservative with respect to charge, (B) expressing said library in mammalian host cells, (C) measuring activity of the encoded receptor or ion channel in said mammalian host cells, (D) identifying those coding sequence(s) which encoded activated receptor or ion channel, wherein said receptor is a multipass transmembrane receptor (claim 4), wherein said receptor is a 7TM receptor selected from a group consisting of: a GPCR, a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, and a polypeptide hormone receptor (claim 5), wherein the activity is measured directly by determining the level of second messengers generated in response to receptor or ion channel (claim 8), wherein the activity is measured by determining the level of transcription from an indicator gene (claim 9), wherein in the indicator gene is an unmodified endogenous gene (claim 10), wherein in the indicator gene is a reporter gene which is directly or indirectly regulated by the receptor or ion channel (claim 11), wherein the level of transcriptional activation of the indicator gene is amplified by expressing one or more intermediate components of the signal cascade leading to the activation of the indicator gene (claim 12), wherein the sensitivity or activity of the indicator gene is modified by manipulating the promoter sequence at the neutral locus for the indicator gene (claims 13-14), wherein the activity of the indicator gene is modified by replacing the transcriptional regulatory sequence of the endogenous gene by that of a heterologous gene (claim 15), wherein transcriptional

regulatory element is derived from that of immediate early genes (claim 16), wherein the transcriptional regulatory element is derived from several heterologous genes (claim 17), wherein the small or medium side-chain amino acids are located at the interfaces between transmembrane (claim 19), wherein the small or medium side-chain amino acids are selected from the amino acids glycine, alanine, serine, asparagine, aspartic acid, cysteine, proline, threonine and valine (claim 20-21), wherein the large and bulky amino acids are selected from trp, his, leu, thr, tyr, asp, cys, phe, pro (claims 22-23), wherein the cell is mammalian (claim 26), and wherein the mutation is identified as an activating mutation if the activity of the polypeptide is increased by at least 2-fold, 5-fold, 10-fold when compared to the activity of the wild type polypeptide (claim 29-31).

Parnot et al teach a method of identifying mutations that constitutively activate a 7TM receptor, the angiotensin II type 1A receptor (abstract). Parnot et al teach a method of constructing a library of mutated receptor by randomly mutating receptor to generate every possible mutations, on average 5 substitutions per residue, and expressing said library in **mammalian cells** e.g., HEK-293 and Chinese hamster ovary (CHO) cells (Mathematical Predictions, and page 7616, right column). Parnot et al teach that methods of site directed mutation to identify constitutive activity are well known in the art (page 7615, left column). Thus, Parnot's teaching include replacing every possible amino acid residue of a 7TM, which encompasses mutating a small, medium or bulky amino acids by conservative mutations, including mutations with respect to charge. Further, the skill of making mutations or conservative substitutions with respect to size, shape and charge is very high (see – column 8, lines 55+ of Wise et al., US

Patent No. 5,981,833 published on 11/9/1999). The reference Wise et al is not applied to support the skill of the art only and not as a prior art. Parnot et al. teach that the constitutively activated receptors have been associated with the physiopathology of 7TMRs, and they are useful for the screening of inverse agonists, ligands that stabilize the inactive conformation (page 7615, right column).

Parnot et al teach measuring activation of constitutively activated receptor by a reporter assay using a luciferase reporter gene construct and by quantitative measurement of IP production (page 7617, left column and Table 1). Further, Parnot et al using aequorin, a luminescent protein, which is sensitive to intracellular calcium mobilization for measuring constitutive activation response of a 7TM receptor (page 7617, left column). Parnot et al teach that a plasmid construct comprising a heterologous gene, aequorin and a doxycyclin inducible element TRE (see page 7616, Materials and page 7617, left column). Parnot et al. teach treating a host cell comprising a vector containing a reporter gene by doxycyclin that would result in the induction of many early genes, and in generation of second messengers that would directly or indirectly induce many genes in said host cell.

Parnot et al teach making and testing a large number of constitutive receptors, and further teach that many of those constitutively active receptors are one hundred fold higher than the wild-type receptor (page 7617, left column and Table 1). It is known in the art that the activation of GPCRs results in the activation of many proteins including early response genes and kinases which play role in generating second messages such as cAMP, IP, and Ca++ responsible in wide variety of patho-physiology (see Moore et

al, US Patent No.5, 683,884, column 4, lines 3+). It is noted that Moore et al is applied to support the skill in the art only. Therefore, Parnot et al explicitly or implicitly teach all the limitations of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Parnot et al in view of king et al (previously applied, Science 250: 121-123, 1990).

Claim 18 is further drawn to a method of identifying constitutively activating mutations in a receptor or an ion channel wherein the reporter gene encodes a gene product selected from a group consist of chloroamphenicol acetyl transferase, beta galactosidase, secreted alkaline phosphatase, a gene product which confers a growth signal, and a gene product for growth media containing aminotriazole or canavanine.

The teachings of Parnot et el are summarized as set forth supra. Parnot et al teach a reporter construct which expresses a luminescent protein. Parnot et al do not teach a reporter construct selected from a group consisting of chloroamphenicol acetyl transferase (CAT), beta galactosidase, secreted alkaline phosphatase, a gene product which confers a growth signal, and a gene product for growth media containing aminotriazole or canavanine.

King et.al. teach that the reconstruction of a heterologous reporter system using the β -galactosidase gene (*lacZ*) in yeast would elucidate understanding of a ligand binding to the G protein coupled receptor and its activation (page 123, left column, last paragraph). King et al. teach that the mammalian β 2-adrenergic receptor is a 7TM receptor. They teach that a high level expression of the receptor is obtained by modifying the front end of the receptor with the NH₂-terminual coding sequence of yeast STE2 gene and placing the receptor under GAL1 promoter (see Fig. 1). Therefore, King et al teach modifying a GPCR by replacing its promoter sequence by a heterologous promoter. Thus, King et al teach constructing a heterologous reporter system by combining the *E.coli* β -galactosidase gene (*lacZ*) under yeast pheromone responsive FUS1 promoter to study G protein coupled receptor activation.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make a heterologous reporter system comprising β -galactosidase gene as taught by King et al. The person of ordinary skill in the art would have been motivated do so to measure the activation of G-protein coupled receptor or ion channel by measuring the change in blue color due to the expression of β -galactosidase gene as taught by King et al. One would have a reasonable expectation of success in making a reporter construct comprising β -galactosidase gene which is routine in the field of molecular biology and further as taught by King et al. Thus, the invention as instantly claimed is *prima facie* obvious in view of combined teachings of the prior art of record.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Parnot et al (2000) in view in view of Moore et al. (US Patent No.5, 683,884, published on 11/4/1997).

Claim 27 is further drawn to a method of identifying constitutively activating mutations in a receptor or an ion channel in a cell, wherein the cell is selected from the group consisting of an avian cell, an insect cell, and a plant cell.

The teachings of Parnot et al (2000) have been summarized as set forth, above. Parnot et al do not teach identifying constitutively activated mutations in receptor or ion channel in a cell selected from the group consisting of an avian cell, an insect cell, and a plant cell.

Moore et al teach identifying modulators calcitonin using host cells such as insect cells, plant cells, amphibian cells, yeast cells or avian cells (column 5, lines42+).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to express the library of coding sequences taught by Parnot et al in a host cell taught by Moore et al. The person of ordinary skill in the art would have been motivated do so to identify a constitutively activated receptors which requires generation of second messengers such as adenlyate cyclase in the host cell via coupling of G protein (column 2, lines 40+). One would have a reasonable expectation of success in using a host cell selected from insect cells, plant cells, amphibian cells, yeast cells or avian cells because these cells are routinely used in molecular biology and biochemistry for drug screening and further because Moore et al teach using such cells for expressing proteins.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Parnot et al (2000) in view in view of Lerner et al. (US Patent No. 6,051,386).

Claim 28 is further drawn to a method of identifying constitutively activating mutations in a receptor or an ion channel in a cell, wherein said cell is a pigment cell which is capable of dispersing or aggregating its pigment in response to an activated receptor or ion channels.

The teachings of Parnot et al (2000) have been summarized as set forth, above. Parnot et al do not teach the use of pigment cells for identifying a constitutive mutation wherein said pigment cell is capable of dispersing or aggregating its pigment in response to an activated receptor or ion channel.

Lerner et al. teach a method of identifying antagonists or agonists for G-protein coupled receptor using a pigment cell. Lerner et al teach that certain chemicals and hormones make changes in signal transduction pathways that involve G-protein coupled receptors. These signal transduction pathways are reflected through changes in the level of cAMP or other second messengers (column 10, lines 7+). They teach that measurement of cAMP (by a direct method) or other messenger (by an indirect method) would facilitate antagonist or agonist identification. They teach that certain chemicals and hormones such as melanocyte stimulating hormone (MSH) and norepinephrine cause pigment dispersion, whereas, melatonin cause an increase in the pigment aggregation in a frog melanophores (column 11, line 17-24).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to express the library of coding sequences taught by Parnot et al in a pigment cell to facilitate measurement through pigment dispersion and aggregation in response to a change in G-protein activation as is taught by Lerner et al. The person of ordinary skill in the art would have been motivated do so to measure the activation a 7TM or an ion channel as the pigment cells provide a number of advantages such as a continuous long term culture growth, can be grown at high density in tissue culture vessels, comprises many endogenous receptors and messengers (see columns 1-2) that would aid identifying constitutive activating mutations. One would have a reasonable expectation of success in using pigment cells because Lerner et al teach using pigment cells in drug screening and 7TM receptor mediated activation.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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